Reply

We appreciate the comments of Dr. Spodick on our study (1). We agree that atrial fibrillation is uncommonly associated with pericarditis, but we believe that there is a relationship between these two conditions in some patients. Many investigators in this field (2–7) also recognize such an association between atrial fibrillation and pericarditis. In a 704-patient study by Davidson et al. (7), pericarditis was reported as the only identifiable condition association with atrial fibrillation in 5 patients (0.7%). We found a similar magnitude of association (3 of 356 patients, 0.8%) in our study. In one of our patients, there was also a history of systemic hypertension, a disorder more commonly associated with atrial fibrillation. In the other two patients (a 27-year old man and a 71-year old woman), no other underlying condition was identified. Given the low incidence of atrial fibrillation with pericarditis, we agree with Dr. Spodick that, for these patients, exclusion of occult cardiac disease is also prudent.

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Interstitial Fibrosis and Angiotensin-Converting Enzyme Inhibition in Patients With End-Stage Myocardial Infarction

Marijianowski et al. (1) have recently investigated the collagen content of noninfarcted myocardium in patients with end-stage myocardial infarction. They report that total collagen levels and collagen type I/III ratios did not differ statistically from those in reference hearts of patients who died of noncardiovascular-related disease. This outcome contrasts with other studies in humans (2–6) and experimental animals (7–10), which have demonstrated an increased interstitial fibrosis in the remote myocardium after infarction and its contribution in the impairment of systolic and diastolic ventricular function (11). However, all patients enrolled in the study of Marijianowski et al. (1) had been treated with angiotensin-converting enzyme (ACE) inhibitors (among other medications), which are known to cause an attenuation of fibrogenesis (3,7,9). Therefore, it is hard to understand that the authors consider it unlikely that ACE inhibition had been truly effective on interstitial fibrosis. Their consideration is based on the argument that other criteria of ventricular remodeling ("extensive myocardial scar formation, with compensatory hypertrophy of viable myocardium and global LV dilation") were still present in these patients.

No quantitative analysis or comparison of these "other criteria" has been presented in this study. Also, it is questionable if, and to what extent, the attenuation of fibrogenesis by ACE inhibition parallels its effects on myocyte hypertrophy during the development of heart failure: the triggers for an increase of interstitital collagen and for myocyte hypertrophy are not the same under all circumstances (4,12) and vice versa the effects of ACE inhibition differ in both processes (12). Finally, we would like to comment upon the authors' interpretation of the results obtained by other groups (see their Discussion). In response to our own study (4), their qualification of microscopic collagenous patches (our Fig. 1A) as "replacement fibrosis" indicative of extended scarring is incorrect for at least two reasons: (1) we excluded such extensions into our noninfarcted myocardial samples microscopically and (2) even if present, isolated microscopic patches of fibrosis are more likely caused by myocyte necrosis due to other mechanisms (13,14).

In conclusion, we regard the results reported by Marijianowski et al. (1) as new evidence that treatment with ACE inhibitors leads to an attenuated interstitial fibrosis in noninfarcted myocardium of patients with (end-stage) myocardial infarction.

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Reply

We appreciate the commentary provided by Drs. Volders and Daemen regarding our work on postinfarct ventricular remodeling (1).

The crux of their critique relates to the fact that our observations deny the widely accepted concept that postinfarct myocardial hypertrophy, as an adaptive phenomenon to the loss of working myocardium, is associated with interstitial fibrosis per se. This concept has led to the inevitable conclusion that the clinical phenomenon of progressive heart failure is because of the increase in extracellular matrix components. Our observations reveal that this sequence of events is not necessarily true. Indeed, the patients reported in our study all presented clinically with progressive heart failure, which necessitated heart transplantation as the only remedy and, interestingly, neither one of these individuals had a significant increase in interstitial fibrous tissue in the noninfarcted hypertrophied myocardium. Hence, the message is that postinfarct remodeling in our patients is not associated with interstitial fibrosis, despite progressive clinical deterioration.

It appears as if Drs. Volder and Daemen wish to ignore the fact that the clinical condition deteriorated despite absence of interstitial fibrosis in the noninfarcted myocardium. Instead, they focus on the potential role of angiotensin-converting enzyme (ACE) inhibitors to "explain" the lack of fibrosis, an aspect that we dealt with in the paragraph "Study limitations." It is of interest that otherwise Drs. Volders and Daemen provide no data to contradict our observations. Thus, we are left with the impression that Drs. Volders and Daemen are biased by their own studies on this subject. Be that as it may, if the use of ACE inhibitors in our patients does account for the lack of interstitial fibrosis in the noninfarcted myocardium, the search for tools to prevent an increase in extracellular matrix and, hence, clinical deterioration is not necessarily the solution in patients with postinfarct myocardial remodeling. This is precisely the point made in our final paragraph.

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Does Earthquake-Induced Cardiovascular Disease Persist or Is It Suppressed After the Major Quake?

We have read the article of Koner et al. (1) with great interest, because their findings that cardiovascular events were suppressed during the 2 weeks following the Northridge earthquake differed from our study on the Hanshin–Awaji earthquake. In our study based on the death information directly obtained from physicians with a 98% response rate, the increase in the cardiovascular events (both cerebrovascular and coronary events) persisted after the major quake for at least a few months (2,3). Coronary artery disease death persisted for 3 weeks after the quake, whereas the stroke death persisted for 5 weeks (Table 1). This discrepancy might in part be due to the degree of stress and the subsequent environmental change in the study subjects. In our study, the subjects were living in one of the most heavily damaged areas, including the epicenter. The study of Kloner et al. (1) included the subjects living in relatively less damaged areas surrounding the epicenter. In addition, the proportion of the elderly subjects in the study area might have affected the different results. We included more elderly subjects in our study because our study region was a community with a large elderly population (31% of the total of 64,000 residents were 60 years old or more). Elderly subjects living in the most damaged area may be more prone to cardiovascular events for a long time after the quake. To clarify the speculation of Kloner et al. (1) that overcompensation may suppress subsequent cardiovascular deaths after a quake, it is necessary to limit the study population to the subpopulation living in the most heavily damaged area, especially the elderly population aged 60 years old or more.

Another very interesting difference was that the stroke death did not increase after the Northridge earthquake. This might be due to the racial differences in the stress-induced phenotype of cardiovascular disease between whites and Japanese. In Japanese, coronary artery disease is much less frequent and stroke is more common, when compared with whites (4). Thus, extreme stress, such as a major earthquake, might trigger cerebrovascular events in Japanese and coronary events in whites. Concurring the stroke death, there might be some delay between the onset and death. Therefore, for Kloner et al.

Table 1. Incidence of Cardiovascular Death in the Tsuna Region after the 1995 Hanshin–Awaji Earthquake

	January*	February	March	April	Total (Jan.–Apr.)
Coronary artery disease	13 (9)	15 (4)	10 (14)	7 (4)	45 (31)
Acute myocardial infarction	11 (0)	4 (3)	8 (2)	5 (1)	28 (6)
Sudden death	2 (9)	11 (1)	2 (12)	2 (3)	17 (25)
Stroke	9 (3)	25 (10)	15 (7)	9 (11)	58 (31)
Cerebral infarction	7 (2)	19 (5)	8 (2)	7 (6)	41 (15)
Cerebral hemorrhage	2 (1)	3 (2)	5 (2)	1 (3)	11 (8)
Subarachnoid hemorrhage	0 (0)	1 (1)	2 (1)	1 (2)	4 (4)
Unclassified stroke	0 (0)	2 (2)	0 (2)	0 (0)	2 (4)
All cardiovascular disease	22 (12)	40 (14)	25 (21)	16 (15)	103 (62)

Parentheses indicate the number of cardiovascular deaths in 1994. *January 17–31.